TROPHOBLASTIC TUMOURS

CHEMOTHERAPY AND DEVELOPMENTS

BY

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This paper reports the results of chemotherapy in patients with trophoblastic tumours during the past five years. Some observations on possible lines of developments in this field are made. A total of 28 patients were seen and 23 were treated. Details of those treated are summarized in Table I.

The decision to use chemotherapy was based on all the data available for each patient. In most instances these data were clinical, radiological, hormonal, and histological, but in some patients tumour tissue was not available for histological examination.

Classification of Treated Patients

Choriocarcinoma.—A diagnosis of choriocarcinoma was made on material from 12 patients, using the criteria of Novak and Seah (1954). Eleven of these had pulmonary metastases and five also had intracranial metastases.

Chorioadenoma Destruens.—Two patients were classified as having chorioadenoma destruens. One had developed pulmonary metastases six months after hysterectomy. The other had no metastases radiographically but had electrocardiographic evidence of pulmonary embolism by tumour.

Unclassified Trophoblastic Tumours.—On histological grounds nine patients could not be classified. The diagnosis in these patients depended essentially on the finding of high gonadotrophin levels in the presence of a disease-complex consistent with tumours of the trophoblast. Seven of these had preceding hydatidiform moles. Six had pulmonary metastases, in three causing severe pulmonary hypertension. Two had intracranial metastases. One of those without recognizable metastases (Case 20) had a pelvic mass 14 cm. in diameter which was shown by angiography to be unusually vascular, even for trophoblastic tumours. This tumour was judged to be inoperable on account of large arteriovenous shunts. Two patients (Cases 14 and 15) had hormonal evidence of persistent trophoblastic disease five and eight months after passing moles and had persistent uterine bleeding which had needed repeated transfusions. Two patients (Cases 1 and 13) in this group had hysterectomy prior to referral for chemotherapy, but in neither instance was a tumour found in the uterus. Both subsequently developed metastases. Seven of the nine patients in this group were judged to have disease which was a threat to life when chemotherapy began, and in six the extent of the disease indicated a probable diagnosis of choriocarcinoma.

Untreated Patients

Five additional patients were seen or referred for chemotherapy. One of these died five days after admission from pulmonary hypertension before the diagnosis of choriocarcinoma was established (Bagshawe and Brooks, 1959). Another patient had been treated with methotrexate intermittently for three years at another hospital, but she died three days after admission without further chemotherapy. Necropsy revealed occlusion of the main pulmonary arteries

TABLE I

Case No.	Age	Parity	Hysterectomy	Oophorectomy	General State on Beginning Treatment	Probable Duration of Disease Prior to Treatment (Months)	Histological Type	Other Features
1	30	4 full-term	+		Poor	25	Unclassified, probable choriocarcinoma	Severe pulmonary hypertension
2	28	1 ,,			Fair	19	,,	,,
3	23	1 ,,			,,	3	Choriocarcinoma	Pulmonary and vaginal metastases
4	22	1 ,,	+	+	,,	4	,,	Pulmonary and other metastases
5	26	1 ,,	+	+	Poor	8	,,	Retinal and pulmonary metastases
6	31	1 full-term. 1 molar	+	+	,,	6	,,	Intracranial and pulmonary metastases
7	29	1 full-term. 1 miscarriage.	+		Fair	3	,,	Pulmonary metastases
8	38	7 full-term	+	+	,,	10	,,	Pulmonary and intracranial metastases
9	33	1 molar			Good	3	Chorioadenoma	E.C.G. evidence of embolism
10	24	2 full-term			Fair	6	Choriocarcinoma	Pulmonary metastases
11	22	1 ,,	+		Poor	5	,,	Pulmonary and intracranial metastases
12	25	Miscarriage	+	+	,,	5	,,	,, ,,
13	27	1 molar	+		Fair	10	Unclassified, probable choriocarcinoma	,, ,,
14	25	1 ,,			Good	8	Unclassified	Persistent uterine haemorrhage
15	18	1 ,,			,,	7	,,	,,
16	23	1 ,,			,,	6	Unclassified, probable choriocarcinoma	Pulmonary and intracranial metastases
17	29	1 ,,	+		,,	12	Chorioadenoma	Pulmonary metastases
18	38	2 full-term. 1 molar			,,	7	Unclassified	
19	24	1 full-term. 1 molar			,,	1	Choriocarcinoma	,, ,,
20	40	1 molar			Fair	5	Unclassified, probable choriocarcinoma	Large vascular pelvic mass
21	23	1 ,,			Poor	6	Unclassified, probable choriocarcinoma	Pulmonary and intracranial metastases and pulmonary hypertension
22	28	1 ,,			Fair	6	Choriocarcinoma	Vascular pelvic mass
23	25	1 molar. 3 full-term			Poor	1	,,	Snowstorm lung fields, pelvic metastases

by tumour. Two patients received small amounts of drugs, but they both died within 48 hours and before therapeutic or toxic effects occurred. One of these patients was in coma from cerebral metastases and also had a perforated duodenal metastasis. The other died from post-hysterectomy complications.

The fifth untreated patient who was referred for treatment had undergone hysterectomy shortly after the evacuation of a hydatidiform mole which had been accompanied by features of a pregnancy toxaemia. Post-operatively she was found to have retinal haemorrhages, and these were attributed to retinal metastases, for which *x*-ray therapy was given to the eyes. When referred for chemotherapy no evidence of residual trophoblastic disease was found, and it seems probable that the retinal haemorrhages were toxaemic rather than metastatic in this patient.

These five patients are not considered further in this paper.

Treatment

Surgical Treatment and Radiotherapy.—Nine patients had had hysterectomy, five with bilateral oophorectomy, prior to referral. One had hysterectomy after the first course of treatment because of moderate uterine haemorrhage and suspected pelvic sepsis. One patient had had radiotherapy to the eyes for retinal metastases prior to chemotherapy. Her sight recovered initially, but later it deteriorated owing to cataract formation and retinal degeneration. Two patients had irradiation to the chest. One of these had become resistant to methotrexate and other drugs, and no benefit was seen from the radiotherapy. The other had a short course of irradiation combined with her first course of chemotherapy. She died shortly afterwards from pulmonary insufficiency. One patient with uterine bleeding had a radium needle inserted in the cervix for the first 24 hours of her initial chemotherapy. The bleeding was negligible after two or three days.

Chemotherapeutic Agents.—The primary drugs used in this study have been the folic-acid antagonist methotrexate and mercaptopurine, used concurrently. Four patients were also given single intra-arterial injections of ethoglucid (triethylene glycol diglycidal ether; "epodyl"). In the three patients in whom drug resistance occurred other drugs were used. These include chlorambucil, nitrogen mustard, tretamine, aminochlorambucil, 6-azauridine, parahydroxyphenone, and actinomycin D.

Regime with Methotrexate and Mercaptopurine.—These drugs were given concurrently in courses of three to five days with a total oral dosage of 75 to 125 mg. of methotrexate and 300 to 3,000 mg. of mercaptopurine per course. Methotrexate was given in five daily doses and mercaptopurine in two or three daily doses. The duration of each course was adjusted according to the patients' toxic signs and white-cell count. The interval between courses ranged from 5 to 27 days but was generally about 10 days. The number of courses in successfully treated patients ranged from 4 to 14, and the duration of treatment was two to seven months. Methotrexate was given intrathecally to four patients with intracranial metastases.

Pelvic Infusion.—After three courses of systemic chemotherapy methotrexate was given to one patient (Case 20) by continuous infusion through a polytetrafluoroethylene (P.T.F.E.; "fluon") catheter of 1-mm. bore which had been introduced via a femoral artery by the Seldinger (1953) technique. The catheter tip was located approximately 2 cm. above the aortic bifurcation. Methotrexate was given at a rate of 50 mg./24 hr. in 500 ml. of saline or 5% dextrose via a Sigmamotor pump. Folinic acid was given by intramuscular route 12–24 mg./24 hr., and mercaptopurine was given by mouth 50 mg. b.d. when the patient was receiving methotrexate. The infusion was given for three periods of five to seven days' duration during a total period of one month. Between infusions patency of the catheter was maintained by heparinized saline, and great care was taken to avoid sepsis at the time of catheter insertion and throughout the period of infusion.

Other Measures.—Patients 16–23 have had dietary restriction of folic acid throughout their period in hospital except for Case 20 during the period of pelvic infusion. The estimated dietary content of folic acid in these patients was generally less than 25 μg./day. Bone-marrow was aspirated under general anaesthesia from the sternum and iliac crests of four patients and was stored in ampoules at −78° C. (Pegg and Trotman, 1959). Autologous marrow was subsequently returned to two patients. Frequent bacteriological examinations of nose, throat, skin, urine, and faeces with appropriate antibiotic therapy were made.

Drug Toxicity.—The side-effects of intensive antimetabolite therapy have been described elsewhere (Hertz *et al.*, 1958; Bagshawe and McDonald, 1960). None of the deaths in this series were attributable directly to drug toxicity such as liver necrosis or gastro-intestinal damage, but bacterial infection was the main cause or a major contributory factor in three deaths which occurred during haemopoietic depression. Twenty of the patients in this series, including the three who died from infectious processes, were treated in open general medical wards.

Gonadotrophin Measurements in Urine

Quantitative gonadotrophin estimations were performed as often as laboratory facilities permitted. During the treatment of the last 10 patients assays were made at least two or three times weekly. These measurements provided prompt evidence of response or resistance to the drugs in use. They also provided a more sensitive and reliable therapeutic target or end-point than other criteria of remission. If it had been possible to measure chorionic gonadotrophin specifically treatment would have continued until zero chorionic gonadotrophin levels were attained. Since the methods used also measured gonadotrophin of pituitary origin the baseline depended on the normal values obtained by the particular method of estimation and on the endocrine status of the patient. The methods used measured either total gonadotrophic activity or chorionic plus luteinizing hormone (I.C.S.H.). With high levels of chorionic gonadotrophin production this lack of specificity was inconsequential. At low levels the pituitary contribution proved important.

The normal premenopausal urinary excretion of gonadotrophin by our methods has been equivalent to less than 100 I.U. of H.C.G./day, although higher rates were sometimes obtained during the middle of the menstrual cycle.

For post-menopausal women the levels were higher and the range wider, and we obtained values equivalent to 400 I.U. of H.C.G./day in recently oophorectomized young women. Oophorectomy widens the range of normal values and thus makes it more difficult to know if the tumour has been destroyed.

In one oophorectomized subject (Case 4) complete remission was thought to have been achieved, but repeated studies showed rising gonadotrophin excretion, and after two months her disease again became active.

In this study from 1958 to 1961 the gonadotrophin excretion was estimated on 24-hour urine collections by the mouse-uterine weight method at the Chelsea Hospital for

Women under the direction of Dr. I. F. Sommerville, and these values are expressed in mouse units. Subsequent estimations were made in this department by mouse-uterine weight and by immunological methods. These values are expressed in terms of the international standard of human chorionic gonadotrophin. The methods used throughout the study have detected gonadotrophins in concentrations equivalent to 0.02 I.U. of H.C.G./ml. or less when used with suitable concentration processes.

Details of the assay methods and values obtained in patients with trophoblastic tumours will be published separately.

Tumour Resistance and Sensitivity

The concept of the sensitivity or resistance of a tumour to a particular agent is widely used in cancer chemotherapy, but for most tumours the concept is poorly defined and usually refers to visible or palpable changes in tumour mass. In the case of trophoblastic tumours this concept can be defined with greater precision by comparison of daily gonadotrophin estimations and the peripheral blood white-cell count. Three broad patterns were seen after courses of treatment. (1) Both the gonadotrophin titre and the white-cell count fell; subsequently the white-cell count returned to normal values before the gonadotrophin levels rose appreciably. (2) Both the gonadotrophin titre and the white-cell count fell; subsequently the gonadotrophin level rose before, or in parallel with, the white-cell count. (3) The gonadotrophin level did not fall but the white-cell count did.

These three patterns of tumour response to a particular drug may be defined as sensitivity, relative resistance, and absolute resistance respectively.

Physical Changes in Tumours During Treatment

Effective chemotherapeutic agents for tumours are apt to provoke dangerous complications. In the case of trophoblastic tumours this has been seen in three situations. (1) Pulmonary embolism has occurred in several patients, in two instances on a substantial scale and accompanied by signs of heart failure. It seems probable from the known ability of these tumours to invade pelvic veins that these veins are the source of the embolism and that the emboli are shrinking necrotic clumps of tumour cells. (2) Several patients with extensive pulmonary metastatic disease have become more dyspnoeic after treatment has started. One patient died despite tracheostomy and artificial ventilation. Since these patients have shown falling gonadotrophin titres and some have subsequently recovered completely, it seems probable that physical changes in the tumour cells, oedema, and cellular infiltration may be responsible for this process. (3) Shortly after starting chemotherapy three patients developed gross neurological defects. Careful neurological examination had previously failed to elicit any abnormality. Necropsy on two of these patients showed extensive necrosis in the cerebral metastases.

It is probable, therefore, that, no matter how effective a chemotherapeutic agent may be against particular tumour cells, such therapy will be ineffective in preventing death if the disease has extended beyond certain limits.

Results

The results are summarized in Table II.

Remissions.—Of the 23 patients treated 17 have been in entire remission since chemotherapy was completed. The remissions range from three months to four and three-quarter years. None of these patients has so far relapsed. One patient had dyspnoea from residual pulmonary hypertension. One has failing vision attributable to *x*-ray therapy. Nine patients have returned to normal menstrual function. One has subsequently had a successful normal pregnancy.

TABLE II

Case No.	Urinary H.C.G. Titre/24 hr. in Mouse or International Units		Methotrexate	Mercapto-purine	Vinka-leukoblastine	Ethoglucid	Chlorambucil	Tretamine	6-Azauridine	Para-hydroxyphenone	Additional Treatment	Duration of Treatment (Months)	Outcome	Duration of Remission (Months)
	Initial	Final												
1	3×10^5 m.u.	<50 I.U.	+	+							Phenindione	7	Full remission	57
2	50,000 m.u.	<50 .m.u.	+	+							"	6	Remission. Residual dyspnoea	56
3	6×10^5 m.u.	<50 I.U.	+	+								5	Full remission	45
4	2×10^6 m.u.	1×10^5 m.u.	+	+	+		+	+	+		DXR	30	Died. Drug resistant	
5	4,500 m.u.	<400 m.u. <100 m.u.*	+	+							DXR to eyes	6	Full remission cataracts	45
6	>2,000 m.u.	<200 m.u.	+	+								2	Died. Epilepsy, pneumonia. Not drug-resistant	40
7	>400 m.u.	<50 m.u.	+	+								4	Full remission	38
8	>1,600 m.u.	<100 I.U.	+	+								5	" "	30
9	>64,000 m.u.	<50 I.U.	+	+								5	Full remission. Subsequent normal pregnancy	19
10	72,000 I.U.	<100 I.U.	+	+								4	Full remission	24
11	3×10^5 m.u.	3×10^6 m.u.	+	+	+							2	Died. Drug-resistant	
12	3×10^6 I.U.	5×10^5 I.U.	+	+							DXR to chest	½	Died. Respiratory insufficiency	
13	$1{\cdot}5\times10^6$ I.U.	4×10^4 I.U.	+	+	+	+			+	+	Phenindione. Nitrogen mustard	8	Died. Relative resistance to drugs. Pneumonia	
14	20,000 I.U.	<100 I.U.										2	Full remission	8
15	8,000 I.U.	<100 I.U.	+	+								2	" "	9
16	28,000 I.U.	50 I.U.	+	+								5	" "	5
17	3,500 I.U.	50 I.U.	+	+		+						4	" "	3
18	2×10^5 I.U.	100 I.U.	+	+								4	" "	3
19	50,000 I.U.	70 I.U.	+	+								3	" "	4
20	32,000 I.U.	40 I.U.	+	+		+					Methotrexate by intra-aortic perfusion	4	" "	3
21	2×10^5 I.U.	50 I.U.	+	+								3	" "	4
22	50,000 I.U.	150 I.U.	+	+		+						3	Died. Staphylococcal infection	
23	2×10^6 I.U.	50 I.U.	+	+								3	Full remission	3

* With oestrogen suppression.

Deaths.—Six patients have died.

Drug-resistant Patients.—Three patients had become relatively resistant to methotrexate and mercaptopurine. Two had responded initially. One of the patients who became resistant (Case 13) had been treated initially with methotrexate alone.

Drug-sensitive Patients.—One of the drug-sensitive patients died from bronchopneumonia in association with repeated epileptic attacks; one from respiratory insufficiency due to confluent pulmonary metastases; and one from staphylococcal infection. This last patient had completed her penultimate course of treatment, and was judged to be in remission from her disease. Necropsy confirmed that her tumour had been destroyed.

Effect of Hysterectomy.—Of the 23 patients in this series 10 had undergone hysterectomy and five of these died. The one death in the 13 patients who had not undergone hysterectomy was that of the patient who died in the final stages of treatment from staphylococcal infection.

Value of Other Drugs.—The value of drugs other than methotrexate and mercaptopurine cannot yet be assessed because of the small number of patients resistant to this drug combination. No instance of complete remission was achieved in this series with other drugs. No benefit was observed from 6-azauridine (0.5 g./day for five days) in two patients, or from parahydroxyphenone (10 g./day for 20 days) in one patient. Transient improvement was seen with actinomycin D (2 patients), chlorambucil (1 patient), vinkaleukoblastine (3 patients). A course of methotrexate followed by vinkaleukoblastine and nitrogen mustard was followed by rapid tumour-shrinkage in one instance, but the patient died from bronchopneumonia.

Effect of Restricted Folic-acid Intake.—The value of restriction of folic acid as practised in Cases 16–23 is difficult to assess because of the small numbers involved. It was noted that the blood count in these patients was somewhat slower to return to normal values after treatment had been in progress for some weeks than in patients on a normal folic-acid intake. No significant drug resistance was observed in the patients on diets restricted in folic acid.

Discussion

Early reports (Hertz *et al.*, 1958) indicated that, although folic-acid antagonists were initially effective against most trophoblastic tumours, an appreciable number subsequently became drug-resistant and death followed. These workers reported complete remission in 28 out of 63 patients with various trophoblastic tumours treated with methotrexate alone. Two additional patients achieved full remission with vinkaleukoblastine (Hertz *et al.*, 1961).

In the present series the use of mercaptopurine in addition to methotrexate arose out of an attempt to reduce or delay drug resistance. In one patient (Case 9) it was demonstrated that a single course of mercaptopurine alone produced a sharp fall in the gonadotrophin excretion (Bagshawe, 1963). The effectiveness of mercaptopurine against trophoblastic tumours has recently received considerable support from a Chinese series (Sung *et al.*, 1963). Mercaptopurine and surgery achieved complete remissions in 28 out of 64 patients judged to have choriocarcinoma and in 24 out of 29 with chorioadenoma destruens.

The small number of patients in the present series restricts statistical comparisons, but the results suggest that the combination of mercaptopurine with a folic-acid antagonist is more effective than either of these agents used alone.

It is sometimes argued that a combination of drugs will have more serious toxic effects than the individual drugs used alone. This, however, is untrue with the drugs used here, because in order to achieve a successful outcome it is necessary to give them close to the limits of tolerance whether they are given singly or in combination.

In the present series those patients who had not had hysterectomy responded more effectively to chemotherapy than those who had had hysterectomy. While several factors determine case selection for hysterectomy, the view that hysterectomy may aid chemotherapy (Chan, 1962) is not supported by this evidence.

Hertz *et al.* (1961) reported complete remissions in 18 out of 25 patients whose treatment began within four months of the onset of symptoms but in only 7 out of 27 patients whose treatment began more than six months after the onset of symptoms. In the present series only five of the patients started chemotherapy within four months of the onset of symptoms, and the sharp distinction in prognosis on the basis indicated by Hertz *et al.* was not seen. However, there is no doubt that the deferral of treatment does increase the hazards, especially in relation to the development of intracranial metastases, which still carry an unfavourable prognosis even when drug-sensitive.

Further Developments

The results so far achieved by chemotherapy in the treatment of these tumours encourages the view that further improvement can be achieved. Two obvious areas for improvement are those of infection control and early recognition and treatment.

Plans are under way to build clean isolation accommodation in a specialized nursing unit for these patients, and it is hoped that the risks of exogenous infection during leucopenic episodes will be substantially reduced as a result of this.

Further reduction of the risks inherent in severe haemopoietic depression may be achieved by greater use of bone-marrow-preservation techniques. The main problem hitherto has been that marrow has to be taken before treatment begins but is not required, if at all, until the late stages of treatment. It is therefore necessary to preserve the marrow by techniques which preserve the viability of the stem cells without significant loss for periods of at least six months.

The method of local infusion of a folic-acid antagonist with systemic folinic acid as outlined in this paper may prove valuable in those patients in whom there is no extra-pelvic disease. A similar technique has been used for tumours of the head and pelvis (Sullivan *et al.*, 1959). The advantages offered by this method are diminished toxicity and risk, together with potentially shorter overall duration of treatment. Since the chemotherapeutic infusion technique can maintain effective drug levels in the pelvic vascular system it is reasonable to anticipate that the method will prove more effective than hysterectomy.

Pelvic infusion of drugs has, however, a potentially greater role as a prophylactic measure for certain patients who have recently had hydatidiform moles and who appear to be candidates for a malignant form of trophoblastic tumour. Evidence from the literature and from patients in the present series indicates that after a hydatidiform mole has been evacuated there are three broad patterns of progress.

In the first group of patients, by far the most numerous, gonadotrophin production falls rapidly to normal values within four to six weeks and there are no sequelae.

In the second group production of chorionic gonadotrophin continues. It may be insufficient at times to give a positive "pregnancy test," although sensitive methods still detect excess gonadotrophin. This evidence of persistent trophoblastic disease is sometimes followed by pulmonary metastases, but after a period of several weeks or months the metastases regress and gonadotrophin production falls to normal values and there are no further sequelae.

In a third group chorionic gonadotrophin production continues, but again may be insufficient at times to give a positive "pregnancy test." After an interval which varies from a few weeks to several years, progressive disease with a histological pattern of choriocarcinoma or chorioadenoma destruens appears.

Unfortunately there is no certain way of distinguishing the second and third groups except by allowing the disease to take its course. The policy of waiting and watching, which is often adopted in this situation, frequently ends in hysterectomy and sometimes in death. Statistical assessment of the value of hysterectomy in such patients is not available. In three cases in the present series hysterectomy did not prevent the subsequent development of distant metastases, and in two of these no tumour was found in the uterus. Such cases do not appear to be uncommon. When tumour is removed by hysterectomy in these patients the gonadotrophin excretion rate falls and this fall may raise the hope that all tumour tissue has been removed. If the tumour has not been completely removed some months may be wasted before this is apparent and other treatment given. Hysterectomy is thus not only ineffective but also disadvantageous in some patients.

The alternative of systemic chemotherapy for all patients with hormonal evidence of persistent trophoblastic tissue after evacuation of a hydatidiform mole is not, however, an attractive one, because of the toxicity and risks which would then be extended to those patients in the second group who could recover without it.

It is therefore suggested that after evacuation of hydatidiform mole quantitative gonadotrophin assays should be performed by a method capable of determining at least 1 I.U. of H.C.G./ml. and preferably less. If, between four and six weeks after the evacuation, excessive gonadotrophin excretion continues, serial assays should be done at weekly intervals. If the gonadotrophin value is not falling progressively six to nine weeks after evacuation of the mole it is suggested that pelvic chemotherapy, by low aortic infusion of methotrexate with systemic folinic acid and a small oral dosage of mercaptopurine, is appropriate. It is, of course, essential that the treatment be carried out with careful attention to sterile techniques and should not be undertaken without the help of quantitative assays. Systemic chemotherapy would then be necessary only in those patients in whom extrapelvic spread has already occurred, as indicated by failure of the gonadotrophin level to fall to normal levels with pelvic chemotherapy.

It is submitted that the method of pelvic infusion as outlined in this paper is worthy of trial in these patients, because the child-bearing capacity can be preserved and because it offers potentially greater therapeutic effectiveness without great risk of toxicity. If this prophylactic effectiveness is proved, then the incidence of choriocarcinoma could be halved. Inevitably this policy involves treating some patients who could recover without such treatment. Even for these patients the four to eight weeks of additional hospital treatment would be at least partly offset by the virtual elimination of the long and anxious follow-up which they undergo at present.

Summary

Twenty-eight patients with trophoblastic tumours were seen or referred for treatment during the past five years, and 23 of them were treated. Nineteen of those treated had pulmonary metastases and eight had intracranial metastases.

Seventeen of the treated patients are in complete remission. The remissions range from three months to four and three-quarter years. Six of the treated patients died. Treatment consisted primarily of repeated courses of methotrexate and mercaptopurine. The value of other drugs and procedures in the treatment of these tumours is being assessed.

One patient was treated with local antimetabolite infusion and intramuscular folinic acid. It is suggested that this method has advantages over other methods for trophoblastic tumours which are confined to the pelvis and for patients with hormonal evidence of persistent post-molar trophoblastic activity.

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